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Treatment of brain metastases of renal cell cancer with combined hypofractionated stereotactic radiotherapy and whole brain radiotherapy with hippocampal sparing

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Abstract. Renal cell cancer patients with brain metastatic disease generally have poor prognosis. Treatment options include surgery, radiotherapy, targeted therapy or best supportive care with respect to disease burden, patient preference and performance status. In the present case report the radiotherapy technique combining whole brain radiotherapy with hippocampal sparing (hippocampal avoidance whole brain radiotherapy HA-WBRT) and hypofractionated stereotactic radiotherapy (SRT) of the brain metastases is performed in a patient with metastatic renal cell carcinoma. HA-WBRT was administered to 30 Gy in 10 fractions with sparing of the hippocampal structures and SRT of 21 Gy in 3 fractions to brain metastases which has preceded the HA-WBRT. Two single arc volumetric modulated arc radiotherapy (VMAT) plans were prepared using Monaco planning software. The HA-WBRT treatment plan achieved the following results: D2=33.91 Gy, D98=25.20 Gy, D100=14.18 Gy, D50=31.26 Gy. The homogeneity index was calculated as a deduction of the minimum dose in 2% and 98% of the planning target volume (PTV), divided by the minimum dose in 50% of the PTV. The maximum dose to the hippocampus was 17.50 Gy and mean dose was 11.59 Gy. The following doses to organs at risk (OAR) were achieved: Right opticus Dmax, 31.96 Gy; left opticus Dmax, 30.96 Gy; chiasma D max, 32,76 Gy. The volume of PTV for stereotactic radiotherapy was 3,736 cm^3, with coverage D100=20.95 Gy and with only 0.11% of the PTV being irradiated to dose below the prescribed dose. HA-WBRT with SRT represents a feasible technique for radiotherapy of brain metastatic disease, however this technique is considerably demanding on departmental equipment and staff time/experience.

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Introduction

Renal cell cancer (RCC) with brain metastases is a disease with poor prognosis (1). The treatment strategy generally depends on the patient performance status, tumor burden and patient preference. The departmental facility device equipment often plays a significant role in the decision making process. Targeted therapy is the mainstay of the systemic treatment at present (2). There are a few viable treatment options with respect to the number of brain lesions, their location and patient overall fitness: Surgical resection, hypofractionated stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT) and symptomatic treatment with steroids (best supportive care (BSC) (3). The main difference between SRS and SRT is in the number of fractions delivered. SRS utilizes only 1 fraction (1 day) for delivery of the whole ablative dose of radiotherapy, which imitates the surgical techniques of treating a patient in one day; whereas, SRT uses 3-6 fractions for treatment dose delivery (4,5). Several prognostic indexes were created to assess the expected patient survival to help clinicians to decide about proper treatment strategy. The recursive partitioning analysis (RPA) index combines the patient's performance status, age and disease burden. One of the greatest disadvantages of this prognostic index is the lack of information about the primary diagnosis with respect to differing prognoses of patients with distinct types of cancer (6). This disadvantage is eliminated by using the graded prognostic assessment (GPA), which is based on age, performance status, presence or absence of brain metastasis and status of extracranial disease with a score from 0 (poor prognosis) to 4 (favourable prognosis) (7). In addition to RPA, this score is influenced by primary diagnosis-type of the cancer. The outcome of these prognostic indexes is the

expected median survival which should be used to drive the decision about the treatment strategy (8,9).

Case report

In April 2013, a 76 year old male patient presented to the Department of Oncology, University Hospital in Olomouc (Olomouc, Czech Republic), with renal cell cancer after resection of the primary renal tumor and also surgical resection of brain metastases within right temporal lobe. The pathology report demonstrated the patient had metastatic clear cell renal carcinoma. Brain recurrence had occurred after the primary treatment (3 metastases in right temporal lobe) 4 months after surgical resection. Computed tomography (CT) ruled out any additional extra cranial disease. The patient was considered to be fit (performance status 1) without significant co-morbidities and SRT radiotherapy with hippocampal avoidance-whole brain radiotherapy (HA-WBRT) was indicated as the appropriate treatment modality after discussion on institutional multidisciplinary board. The patient did not receive any targeted therapy prior to or during the radiotherapy dose delivery. Planning CT scans with 2 mm slide thickness were created. The International Commission on Radiation Units and Measurements (ICRU) recommendations number 50, 62, 83 were followed during the target volumes delineation, treatment plan calculation and plan approving process (10-12). For SRT, the metastatic disease was contoured based on the fusion with T1 weighted sequences magnetic resonance imaging (MRI) as gross tumor volume (GTV) with adding the 2 mm margin to create the clinical target volume (CTV) and the planning target volume (PTV). The Monaco planning system (IMPAC Medical Systems, Maryland Heights, MO, USA) with Monte Carlo computing software (version 3.30.01; Elekta, Stockholm, Sweden) was used for treatment plan calculation and Elekta Synergy linear accelerator (Elekta) with single arc volumetric arc radiotherapy (VMAT) with 6MV photon energy was used for treatment dose delivery. The prescribed dose was 21 Gy in 3 fractions delivered on 3 consecutive days with a biologically effective dose (BED10) of 35.7 Gy. The dose was prescribed on isodose selected as isodose most accordingly encompasses the PTV without any limitation regarding the maximum dose within the PTV (Fig. 1) and with the maximum dose drop off towards the surrounding normal structures. A HeadSTEP system with thermoplastic mask (Elekta) was used for patient immobilization. Patient position verification was achieved by three cone-beam CT (CBCT) every single day of the treatment. First CBCT was carried out after patient placement on the treatment table and position was adjusted using HexaPOD setup system (Elekta), a second round of CBCT followed after position adjustment to confirm proper positioning and a third round of CBCT followed the delivery of the treatment to rule out any intrafractional (during the dose delivery) shifts. The volume of final PTV was 3,736 cm^3, created as the sum of 3 metastases volumes, with a minimum dose covering 100% of the PTV D100=20.95 Gy and only 0.11% of the PTV volume being irradiated to dose bellow prescribed dose. HA-WBRT was continued after completion of SRT. For contouring and plan review purposes RTOG 0933 '*(*a phase II trial of hippocampal avoidance during whole brain radiotherapy for brain metastases*)*' proposals were followed aiming to reach the limit

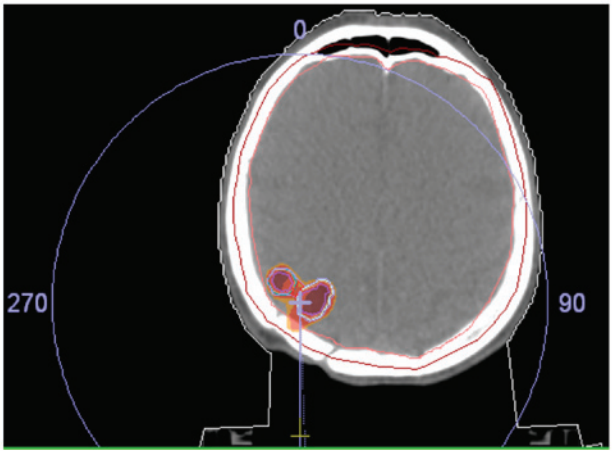

Figure 1. Dose distribution of fractionated stereotactic radiotherapy.

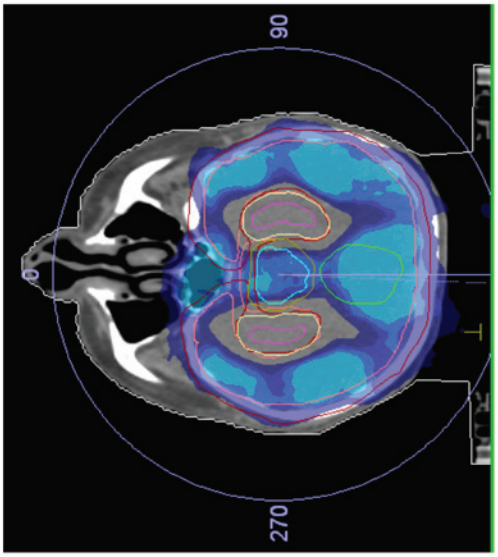

Figure 2. Dose distribution of hippocampal avoidance-whole brain radiotherapy.

to the maximum dose to hippocampal structures to 17 Gy and D100 to <10 Gy (the dose to 100% of hippocampus should be kept under 10 Gy) (13). Hippocampal structures were delineated after fusion with MRI and a 5 mm margin was added to the final contours of the hippocampus. The whole brain CTV was contoured manually including the whole brain and an additional margin of 5 mm was added to create PTV. The WBRT PTV excluded hippocampal structures within the 5 mm margin creating the HA-WBRT PTV. The prescribed treatment dose was 30 Gy in 10 fractions (Fig. 2). The immobilization techniques for HA-WBRT were the same as for SRT and the treatment plan was prepared with similar planning systems as described above for SRT with following results: (near max) D2=33.91 Gy, (near min) D98=25.20 Gy, D100=14.18 Gy, D50=31.26 Gy, homogeneity index (HI) calculated as D 2-D 98/D 50 was 0.278. The maximum dose for hippocampus was 17.50 Gy and the mean dose of 11.59 Gy did not exceed the RTOG 0933 trial constrains. The following doses to OAR were achieved: Right optic nerve D max 31.96 Gy, left optic nerve D max 30.96 Gy, chiasma D max 32.76 Gy. The dose was delivered in 10 consecutive

working days within 2 weeks without any unintentional time gaps. CBCT was performed weekly to verify patient positioning on the treatment table. A low dose of oral steroids (dexamethasone, 3 mg/day) was administered during the whole duration of radiotherapy. As a part of quality assurance process in the department all contours and treatment plans were reviewed by a second experienced clinical oncologist. The patient received the treatment without significant acute toxicity however longer follow up regarding late toxicity, progression free survival and overall survival is needed to confirm the long term safety and effectivity of this treatment technique.

Discussion

Expected patient survival may be used to guide clinicians about proper treatment strategy. Generally patients with an expected median survival <3 months should not be exposed to potential risks of surgery or stereotactic radiotherapy since the cost/benefit ratio of these treatment modalities is questionable in this group of patients and simple radiotherapy technique such as two opposed lateral fields using conventional simulator should be considered. Several clinical trials have evaluated which treatment option or their combination is most appropriate for patients with brain metastatic disease (3).

Surgery represents the mainstay of local treatment of brain metastatic disease. Surgical resection may be used as the sole technique or in combination with WBRT after resection or SRT; SRS may be used on the surgical cavity after the resection. WBRT after the surgical resection decreases the risk of disease recurrence however this advantage doesn't project into overall survival benefit suggesting the possibility of deferring the WBRT, SRS or SRT for the time of disease recurrence (14-18). By contrast, SRT with WBRT compared with WBRT alone increases the overall survival of treated patients, indicating that these treatment modalities should be combined. Again when comparing SRS alone with SRT, and SRS with WBRT, the overall survival rate remains the same, however the chance of local recurrence decreases by ~30% when WBRT is added (19-30). Another issue related to WBRT is the potentially increased risk of cognitive function impairment (30). There are data suggesting that hippocampal structures (mainly the subgranular zone of the hippocampus) are highly susceptible to radiotherapy injury and these changes may be responsible for cognitive (learning, memory and judgement) worsening after WBRT (31-33). Cognitive impairment in patients achieving longer survival may significantly deteriorate the patient quality of life even if actual function tests to accordingly assess neurocognitive functions are questionable (mini mental status exam, Hopkins Verbal Learning Test, CogState computerized neurocognitive tests) and one can suggest that the neurocognitive deterioration may be caused by subclinical metastatic disease progression in the brain which is indistinguishable from radiotherapy toxicity. Similar to SRT, SRS may be used as the sole technique or in combination with WBRT with similar advantages and disadvantages. It is important to note that the dose of the SRT or SRS should be decreased by 10-20% when combined with WBRT to avoid extensive brain toxicity. Clinical trials directly comparing surgery and SRT are not convincing for preference of either of these techniques (34), however one has to consider the morbidity of brain surgery with respect to patient overall fitness and co-morbidities. In addition, the optimum timing for SRT, SRS, WBRT, and HA-WBRT is not very clear considering that immediate WBRT following SRT, or SRS, may significantly increase the toxicity of radiotherapy. In cases of WBRT preceding SRT/SRS, complete remission of certain small metastatic lesions may occur and thus, no metastasis may be visible on planning scans for SRT/SRS and the opportunity for SRT/SRS could be missed. There are data suggesting that deferred WBRT may not reverse neurological deficit caused by brain recurrence (35) making the decision about proper WBRT timing even more difficult. The most recent recommendation regarding WBRT published in The Lancet Oncology suggested indication of SRS, SRT without WBRT as the preferred technique if feasible (36).

For patients with an expected survival time of <3 months, WBRT or best supportive care (BSC) with oral steroids remains a viable option (3,37). The dose of the steroids is another possible issue without clear recommendation however the dose should be driven by neurological symptoms also taking into account the side effects of long term steroid treatment. One of the possible technique how to avoid above mentioned unwanted side effect of WBRT is to perform HA-WBRT avoidance (35,38). Considering radiotherapy of hippocampal structures is considered to be responsible for cognitive impairment its avoidance could possibly preserve the cognitive functions. One argument against this technique is that there is an increased risk of disease recurrence in the areas that radiation is avoided. However, Ghia *et al* (39) concluded that the risk is low and clinically insignificant after assessing the risk or metastatic disease in the hippocampus with 5 mm margin. Furthermore, the potential recurrence in this area may be treated by SRT or SRS. The Clinical trial Radiation Therapy Oncology Group RTOG 0933 was initiated to confirm this expectation utilizing HA-WBRT (excluding germ cell tumors, small cell lung cancer and hematologic malignancies) using Hopkins Verbal Learning Test-Revised for cognitive functions assessment (13), however no final results are published at present. When considering bringing HA-WBRT into daily practice one has to take into account the departmental equipment, staff time and experience resulting in the significantly higher cost required for target volumes delineation, calculation of VMAT treatment plan and treatment delivery comparing with simple and quick technique such as 2 lateral opposed fields using conventional simulator for WBRT. This decision should be guided by best clinical judgement, the above mentioned prognostic indexes with respect to expected patient survival and departmental technical equipment. One of the unanswered question in the case of SRT indication is the role of systemic treatment. More specifically if the management should follow the guidelines for surgical resection, which means in the case of renal cell cancer metastasis continuing with observation and waiting to administer systemic treatment only in the case of disease progression or commencing targeted therapy immediately after ablative radiotherapy. No randomized data or recommendations exists regarding this issue and decision should be made on an individual basis (27,40).

SRT with HA-WBRT represents a feasible and safe technique for the management of brain metastatic disease.

Due to the increasing overall survival rates among cancer patients, sparing of cognitive functions may be even more significant in the future.

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